276th ENMC International Workshop: recommendations on optimal diagnostic pathway and management strategy for patients with acute rhabdomyolysis worldwide. 15th-17th March 2024, Hoofddorp, The Netherlands

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ABSTRACT

The 276th ENMC International Workshop on rhabdomyolysis brought together 21 experts to address the compelling need for standardized guidelines on the clinical approach of rhabdomyolysis. There was a general agreement that a diagnosis of rhabdomyolysis require that **1)** clinical symptoms include severe muscle swelling, weakness and/or myalgia; **2)** serum CK-levels exceed 10,000 IU/L in case of exertional, and >5000 IU/L in non-exertional rhabdomyolysis; **3)** CK-levels reaching a maximum 1–4 days after the event and normalizing to baseline within 1–2 weeks of rest. In case of an underlying neuromuscular condition, CK-levels should exceed 5–10 times the patient's baseline level. Treatment should be initiated only in case of high risk on acute kidney injury, which can be predicted by the McMahon score. Furthermore, recommendations on performing genetic testing were formulated and the use of the 'RHABDO'- acronym was generally agreed upon as a tool to aid clinicians in deciding which patients require genetic testing. Moreover, recommendations on follow-up were made, with a particular emphasis on evaluation of physical and psychological sequelae. Patient representatives present during the workshop emphasized the importance of the current recommendations for future clinical guidelines on rhabdomyolysis.

1. Introduction and overview

The 276th ENMC International Workshop was held from March 15 to March 17, 2024. A total of 21 physicians and researchers from 12 different countries (Australia, Canada, Denmark, France, Germany, Italy, Iran, The Netherlands, Spain, Sweden, UK, USA) attended the workshop, as well as two patient representatives. The aim of the workshop was to define an optimal diagnostic pathway and management strategy for patients with exertional rhabdomyolysis (ERM).

Rhabdomyolysis is a complex and potentially life-threatening condition, involving rapid dissolution of damaged or injured skeletal muscle. Clinical manifestations range from mild myalgia with elevated serum creatine kinase (CK) levels to severe acute renal failure (ARF), compartment syndrome, electrolyte disturbances, cardiac dysrhythmia and disseminated intravascular coagulation. Despite the relevance to many medical disciplines and the complexity and severity of complications, there is no established formal definition or well-defined diagnostic strategy guidelines for rhabdomyolysis. Although rhabdomyolysis is defined as a clinical syndrome of severe myalgias, muscle weakness and muscle swelling in the presence of a sudden elevation and

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subsequent fall of CK levels, the CK cut-off value used in previous studies varies greatly from 1000 IU/L to 10,000 IU/L [1–4]. In addition to the diagnostic assessment in the acute setting, a proportion of patients require further analysis to identify a possible underlying genetic defect contributing to the susceptibility for developing rhabdomyolysis. Several Mendelian genetic defects have been associated with increased rhabdomyolysis susceptibility. These include variants in genes involved in muscle metabolism and mitochondrial function (e.g., *ACADVL, CPT2, PYGM* or *LPIN1*), associated with muscular dystrophies, or related to Ca^{2+} homeostasis and excitation-contraction coupling (e.g., *RYR1*) [5, 6]. Although the means to detect a genetic contribution have increased markedly since the introduction of next generation sequencing, the wide genetic heterogeneity potentially contributing to rhabdomyolysis susceptibility poses a considerable diagnostic challenge for clinicians. The complex interplay between risk factors and possible genetic susceptibility (Fig. 1) requires a standardized diagnostic approach, including a formal definition of rhabdomyolysis, and recommendations on how to select patients that require further genetic investigation (Fig. 2) [7,8].

The main aim of this workshop was to reach consensus on the optimal diagnostic pathway and management strategy for patients with ERM. We aim to develop guidance on management during recovery of rhabdomyolysis and enhance secondary prevention in patients with genetic susceptibility.

1.1. Session 1: various causes of rhabdomyolysis

John Vissing (Denmark) introduced the workshop, outlining its main deliverables and providing a historical overview of rhabdomyolysis and its contributing factors. Rhabdomyolysis has gained increasing attention over the past century due to its potential to cause severe ARF, sometimes requiring dialysis [9]. Rhabdomyolysis related ARF is multi-factorial and is the result of both intrarenal vasoconstriction and toxic effects of myoglobin and its byproducts on kidney cells which may result in renal tubule obstruction [10]. External triggers for rhabdomyolysis include prolonged immobilization, substance abuse, seizures, physical exertion, and adverse drug reactions, which are more commonly encountered in emergency settings than in neuromuscular clinics [11].

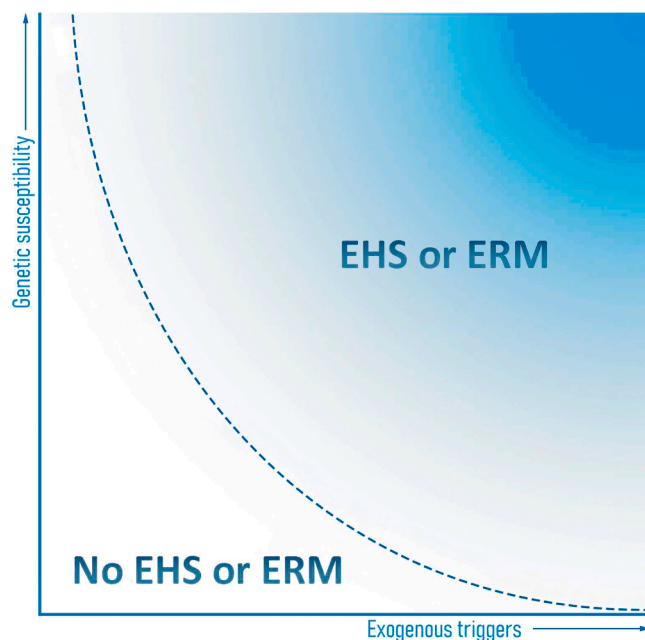**Nicol Voermans** (The Netherlands) gave a presentation on ERM,

Fig. 1. Interaction between genetic susceptibility and external triggers. Figure adapted from Kruijt et al. [7]. EHS = exertional rhabdomyolysis, ERM = exertional heat stroke.

noting that strenuous exercise is a common trigger. Although it can signal an underlying neuromuscular issue, it more frequently affects healthy individuals exposed to unaccustomed exertion, for example military recruits or individuals restarting high intensity exercise after a break. Kenney et al. studied 499 healthy recruits and found that CK levels peaked on day 7 of basic training, with 27 % exceeding 5 times the upper limit of normal (ULN) and 11 % exceeding 10 times the ULN, reaching up to 35,056 IU/L, and returned to normal at day 14 [12]. However, raised CK levels did not necessarily correlate with the presence of symptoms of ERM (e.g., myalgia, muscle swelling or signs of ARF). Therefore, raised CK levels <50 times the ULN (e.g., <10,000 IU/L for white females) can indicate a physiological response to exercise that shouldn't prompt further investigation. Furthermore, Bäcker et al. published a review of 772 patients and reported that ERM was most common in young males during running (54 %) and weightlifting (15 %) events [13], while Eichner highlighted "team rhabdomyolysis" outbreaks in group sports (e.g., football) [14]. Many of these examples of ERM occurred as a result of pressure from coaches, pushing athletes beyond safe limits. Based on these previous studies, the RHABDO acronym was developed as a tool to guide neuromuscular screening referrals (Box 1) [15–17].

Pascal Laforet (France) discussed exercise intolerance in glycogenosis. Patients with defects in glycogenolysis or glycolysis often experience muscle fatigue and discomfort and exertional symptoms from infancy, sometimes followed by exercise-induced contractures and rhabdomyolysis, with fatigue and myalgia resolving after several minutes of rest. Glycogen storage disease (GSD) 5 (McArdle disease) is the most common muscle glycogenosis disorder [18]. In this group of patients, a non-ischemic forearm exercise test measuring lactate and ammonia can be a helpful screening tool to aid diagnosis; blunted lactate production and/or elevated ammonia levels are key indicators. While CK rises acutely during rhabdomyolysis, the baseline CK is almost always raised. Routine lab tests can aid diagnosis, such as elevated bilirubin and reticulocyte count in GSD 7 and 9d, or hyperuricemia in GSD 5 and 7 [19,20]. Although next generation sequencing (NGS) panels are widely available, the clinical history supported by genetic testing and biochemical enzyme analysis in some situations (e.g., when genetic testing reveals a VUS) remain crucial to avoid misdiagnosis. Increasingly easy access to NGS gene panels must not overshadow the importance of clinical and biochemical phenotyping of patients (biochemical analysis in erythrocytes for phosphofructokinase, phosphoglycerate kinase, and aldolase A deficiencies), knowing that detection of variants in the known genes should always be compared to clinical symptoms to avoid misdiagnosis. For example, muscular dystrophies can mimic glycogenosis with symptoms of exercise intolerance and persistent hyperCKemia ("pseudo-metabolic" phenotypes).

Salman Bhai (USA) and **Farzad Fatehi** (Iran) talked about rhabdomyolysis in fatty acid oxidation disorders (FAODs), a group of rare metabolic conditions impairing fatty acid metabolism for energy. FAODs often present with symptoms triggered by fasting or illness, including cardiac issues (cardiomyopathy, arrhythmias), muscle symptoms (like rhabdomyolysis), and liver problems (hypoglycaemia, hepatomegaly) [21]. Common FAODs include MCAD deficiency (1 in 10,000–20,000 newborns), LCHAD deficiency (with severe cardiac, muscle, and liver symptoms), and VLCAD deficiency (causing cardiac and muscle weakness) [22]. Rhabdomyolysis is common in FAODs due to insufficient energy substrates during prolonged exercise, fever and fasting. Diagnosis includes finding elevated acylcarnitine and fatty acid metabolites [23]. Strategies include avoiding triggers, such as avoiding prolonged exercise and fasting, providing alternative energy sources (e.g., reducing dietary fat and increasing dietary carbohydrate) [24–26]. In addition, carnitine and coenzyme Q10 supplements may be beneficial in certain subtypes [21]. Diagnostically, once a FAOD is suspected, molecular testing is an efficient tool that can be supported by biochemical labs and/or if the results include variants of uncertain significance [25]. Diagnosis is essential to optimize management, provide genetic
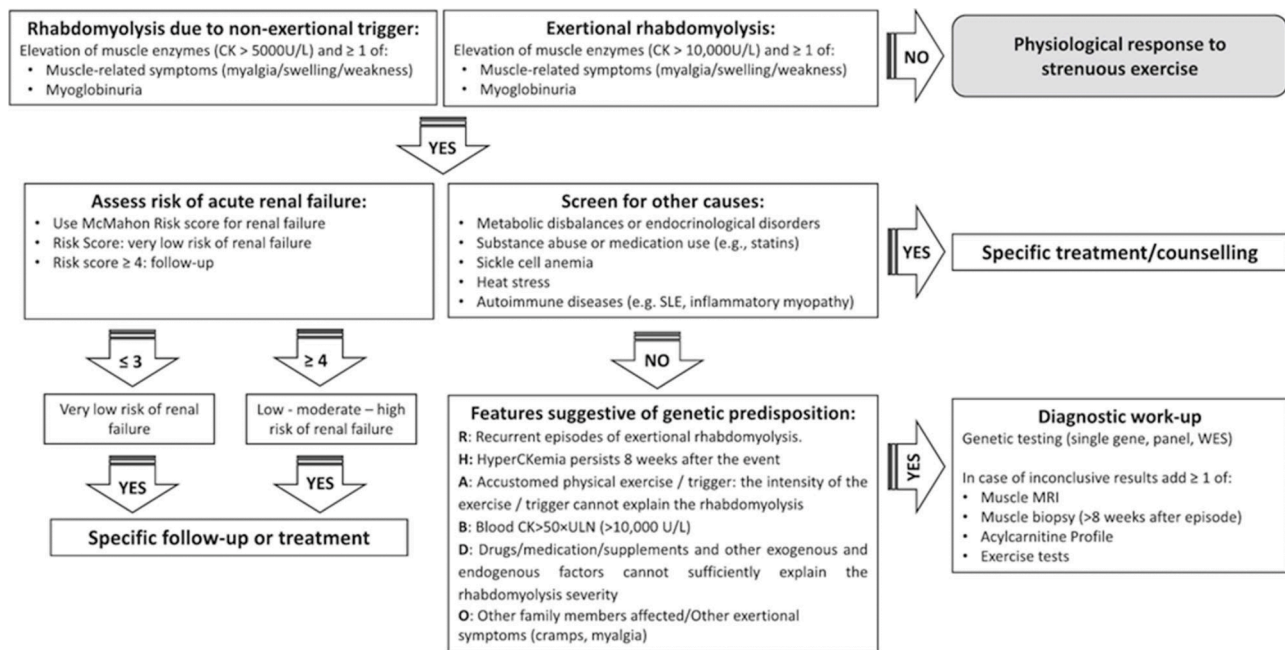
Fig. 2. Flowchart for screening and treatment of adult patients with rhabdomyolysis. Figure adapted from Voermans et al. [8]. CK=creatine kinase; SLE=systemic lupus erythematodes; ULN=upper limit of normal; WES=whole exome sequencing.

Box 1

Consider a genetic cause of the ERM in case of any of the 'RHABDO' features are present.

R: Recurrent episodes of ERM;

H: HyperCKemia persists 8 weeks after the event;

A: Accustomed physical exercise: the intensity of the exercise cannot explain the rhabdomyolysis event;

B: Blood CK>50 × ULN (>10,000 ULN);

D: Drugs/medication/supplements and other exogenous and endogenous triggers cannot sufficiently explain the rhabdomyolysis severity;

O: Other family members affected/Other exertional symptoms (cramps, myalgia).

counselling, and identify patients for research opportunities.

Gabriele Siciliano (Italy) presented the topic of mitochondrial dysfunction in rhabdomyolysis pathophysiology, noting the importance of mitochondria in maintaining skeletal muscle energy homeostasis by adaptive re-programming to meet demands imposed by physiologic or pathophysiological stresses [27,28]. Primary inherited mitochondrial disorders (PMDs), caused by mutations in nuclear (nDNA) or mitochondrial DNA (mtDNA) genome, are a clinically heterogeneous group of disorders that arise due to direct or indirect dysfunction of the mitochondrial respiratory chain, often showing multisystemic symptoms with muscle involvement, triggered by prolonged aerobic physical activity [28–31]. Rhabdomyolysis or myoglobinuria have been reported in both nDNA (*DGUOK, FDX1L, HADHA, HADHB, ISCU, FDX2,* and *CoQ10*) and mtDNA (*MT-CO1, MT-CO3, MT-CYB, MT-ND1*) related PMDs. Notably, the phenotype of patients with *ISCU* or *FDX2* variants is mainly limited to skeletal muscle and has been associated with recurrent rhabdomyolysis [32,33]. Furthermore, drug-induced rhabdomyolysis has been reported in PMDs (e.g., after exposure to suxamethonium in *MT-ND1*, or propofol in *POLG1*) [34,29,30], as well as in lipin-1 deficiency [35]. In conclusion, both nDNA and mtDNA gene polymorphisms have been postulated as risk factors for rhabdomyolysis [29].

Benedikt Schoser and **Felix Kleefeld** (Germany) discussed rhabdomyolysis definitions and the occurrence of rhabdomyolysis in limbgirdle muscular dystrophies (LGMD). Their 2020 systematic review of 614 studies indexed in PubMed and Embase (1968–07/2018) found that 38 % defined rhabdomyolysis commonly by using a CK cut-off value >5 × ULN in 23 % and >1000 IU/L in 28 % of studies [4]. Definitions often included elevated CK with no set threshold, clinical symptoms, and exclusion criteria for myocardial, renal, cerebral, and neuromuscular

factors. Severe rhabdomyolysis was defined by myoglobinuria and ARF. Analysis revealed that most reports used a definition of rhabdomyolysis as a clinical syndrome of acute muscle weakness, myalgia, and muscle swelling combined with a CK cut-off value of >1000 IU/L or CK >5 × ULN. A recent PubMed search identified only 14 papers reporting on rhabdomyolysis in the context of muscular dystrophies, mainly dystrophinopathies, *RYR1*-related diseases, and metabolic myopathies. LGMDR12, LGMDR9, and LGMDR3 were the most common LGMD subtypes linked to rhabdomyolysis, though CK elevation is common in LGMD and doesn't always indicate rhabdomyolysis, emphasizing the need for adjusted CK cut-off values in these patients [36].

Nicol Voermans (The Netherlands) highlighted the role of *RYR1* gene variants in rhabdomyolysis. *RYR1* variants are associated with a wide spectrum of inherited myopathies presenting throughout life, including the pharmacogenetic disorder malignant hyperthermia (MH). Interestingly, *RYR1* variants that have been linked to MH susceptible (MHS) accounted for up to 30 % of ERM in a series of unrelated families with rhabdomyolysis and/or exertional myalgia [37–39]. Most frequent triggers included exercise, exposure to hot ambient temperatures, infection in the days prior to the event, consumption of alcohol or use of illicit drugs. Affected individuals often experience post-exercise myalgia and muscle stiffness and lack a family history of neuromuscular symptoms. Recognizing *RYR1*-related rhabdomyolysis is essential for counselling and adapting training, despite challenges with variant pathogenicity and variable penetrance. The case of a semi-professional cyclist illustrated many of these aspects [40]. He shared his experiences in the 259th ENMC workshop on anesthesia in neuromuscular disorders and pointed out the importance of (sport)psychological support in the process of changing his career from sports to a white-collar

career [41]. Furthermore, a prospective study of 40 individuals with *RYR1*-related MHS or ERM demonstrated a high prevalence of neuromuscular symptoms. Patients should be informed about these neuromuscular manifestations to reduce unnecessary consultations with other healthcare professionals and additional diagnostic investigations, since they do not necessarily reflect a second pathology [42]. Ibarra Moreno et al. performed a database review of 164 MHS patients who received oral dantrolene for myopathic symptom relief and most patients reported improvement of neuromuscular symptoms and adhered to therapy [43]. These findings underscore the need for timely diagnosis of potential genetic susceptibility.

Vandana Gupta (USA) talked about the complex interplay between environmental and genetic factors contributing to the development of rhabdomyolysis. Extrinsic factors contributing to rhabdomyolysis are mostly identified through life-threatening reactions to different triggers in the general population [44]. A study of 833 patients found that 30 % had a single trigger, 40 % had 2–4 triggers, and 30 % had no identifiable trigger, with higher CK levels being associated with the higher number of triggers. Genetic analysis of known genes revealed pathogenic variants in metabolic and calcium-regulating genes. New models as the *TANGO2* morphant zebrafish help to demonstrate rhabdomyolysis susceptibility [45]. While these zebrafish show normal skeletal muscle function without any extrinsic triggers, exertion leads to severe muscle breakdown. This research emphasizes the importance of clinical records, genetic analysis, and in vivo models for better diagnosis and disease management [45].

Ros Quinlivan (United Kingdom) provided an overview of acute rhabdomyolysis in children, which is relatively rare, but can occur in neuromuscular and metabolic disorders. A review of 534 pediatric cases (ages 0–18) showed a male predominance (62–70 %) and identified infection as the most common cause, particularly viruses like influenza A and Coxsackie B [46–49]. Trauma, unaccustomed exercise and use of illicit drugs including 3,4-Methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD) and cocaine were the most likely causes in older children and adolescents [46,50]. Risk factors for rhabdomyolysis include epilepsy, neuropsychiatric disorders requiring medication, and nutritional deficiencies [46,47,50,51]. The classic symptoms of myalgia, weakness, and myoglobinuria are often absent in very young children [46,47], with myoglobinuria reported in only 3–6 % of cases [46,47,50–52]. Risk indicators for ARF include elevated CK levels, dehydration, and metabolic disturbances. The need for renal replacement therapy was more likely related to the underlying cause such as sepsis and the incidence was as high as 30 % for those admitted to PICU, but as low as 5 % for the whole cohort [46,50]. Prognosis appears to be particularly poor for children who have ARF related to acute diabetic ketoacidosis, in one study renal replacement therapy was required in 30 % and mortality in this group of patients was as high as 50 % [53]. Overall, prognosis for children presenting with ARF was excellent with almost all children making a full recovery, with only 2 % in one cohort developing chronic renal impairment related to the underlying disease rather than to rhabdomyolysis [46].

1.2. Session 2: current diagnostic strategy

Nick Kruijt (The Netherlands) and **Mads Godtfeldt Stemmerik** (Denmark) presented findings from an online survey among members of the ERN EURO-NMD on the current diagnostic approach and management of ERM. Nineteen responses from eleven countries (covering neurology, pediatric neurology, and medical genetics) revealed variability in diagnostic tools used beyond genetic testing, including muscle MRI, muscle biopsies, muscle ultrasound, exercise testing, and neurophysiological tests. Rhabdomyolysis severity was assessed primarily through laboratory (90 %) and clinical evaluation (84 %). A total of 73 % scheduled a follow-up, however, only few members reevaluated the patient after 12 months. Referral of patients was inconsistent, with common referrals to nephrologists, cardiologists, and geneticists, but no

consensus on CK cut-off levels, which ranged from 1000 to 20,000 IU/l. The most common answer (28 %) was 10,000 IU/l, but levels between 1000 IU/l and 20,000 IU/l were provided. Overall, the survey found no coherent diagnostic or management approach to rhabdomyolysis among members of the ERN EURO-NMD network.

Nathalie Roux-Buisson (France) outlined the critical role of molecular diagnosis in rhabdomyolysis, which can be essential for targeted management. In addition to the previously discussed genetic heterogeneity contributing to rhabdomyolysis susceptibility, more recent studies expanded the genetic landscape and identifying variants in *MLIP, MYH1*, and *OBSCN* to be associated with rhabdomyolysis [17,54,55]. The PanelApp platform offers a gene panel for acute rhabdomyolysis (66 genes, 53 validated) and another for rhabdomyolysis and metabolic muscle disorders (72 genes, 62 validated). Additionally, ClinGen provides Expert Panels for congenital myopathies and fatty acid oxidation disorders but currently lacks one specific to rhabdomyolysis. Studies using NGS revealed varied clinical presentations, from asymptomatic hyperCKemia to ERM and persistent muscle weakness, with diagnostic methods ranging from targeted panels to whole-exome sequencing. Positive yields can range from 15–50 % for (likely) pathogenic variants [7], with *RYR1* as the most frequent gene implicated [56,57], and findings of oligogenic inheritance emerging as well [58]. Data from the Grenoble hospital laboratory aligns with these findings, showing a 20 % genetic positive yield, predominantly with *RYR1* variants. This highlights the importance of precise phenotyping and comprehensive NGS, using large gene panels, exome or genome sequencing, and mtDNA analysis, to improve diagnostic accuracy and guide patient management.

Gina Ravenscroft (Australia) gave an overview of the current evolving genetic landscape of ERM, highlighting that variants in muscular dystrophy and myopathy genes may predispose individuals to this condition (Fig. 3) [17]. New genes, including *MLIP, MYH1* and *OBSCN* [54] have also been linked to rhabdomyolysis [55,59]. In an Australian/New Zealand GSD/rhabdomyolysis cohort (n=765), the diagnostic yield was 17.5 % using a comprehensive targeted neuromuscular disease gene panel, with the most frequent genetic findings including *RYR1, PYGM, DMD*, and *ANO5*. A copy number variant accounted for 12 % of the diagnoses (unpublished data). In a research cohort (n=78), the most frequent trigger was exercise (55 %) and four patients had a history of malignant hyperthermia. The genetic diagnostic yield in this research cohort following panel screening was 22 % (unpublished data). Patients with a family history had a 70 % diagnostic yield, while isolated cases had a 9 % diagnostic yield. There was no difference in diagnostic yield when patients were stratified by peak CK (5–50x ULN compared to >50x ULN) or when comparing patients with a single episode to those with recurrent episodes. Over 40 % of patients showed variants of uncertain significance (VUS), often in *CACNA1S* and *SCN4A*, with 57 patients having VUS in multiple rhabdomyolysis-associated genes, suggesting the possibility of oligogenic inheritance [60]. Recent findings in *OBSCN* suggest it could underlie many unexplained cases [61]. Advances in whole-genome sequencing and RNA-seq will likely uncover more genetic causes, and large case-control studies will be crucial for exploring the oligogenic nature of this condition.

Anders Oldfors (Sweden) presented the role of muscle biopsy in the acute phase of rhabdomyolysis. Muscle biopsy is sometimes performed to differentiate between inflammatory myopathies, toxic myopathies and other causes of rhabdomyolysis [62]. In cases where inflammatory myopathy is suspected, histopathological features combined with myositis-specific autoantibody testing can confirm or rule out an autoimmune component. When autoimmune causes are excluded, biopsies taken in the recovery phase—weeks to months after a rhabdomyolysis episode—can reveal metabolic or dystrophic abnormalities underlying the condition. In acute rhabdomyolysis, muscle biopsy typically shows fiber necrosis and regeneration from satellite cells, with immunohistochemical staining for embryonic myosin heavy chain indicating a
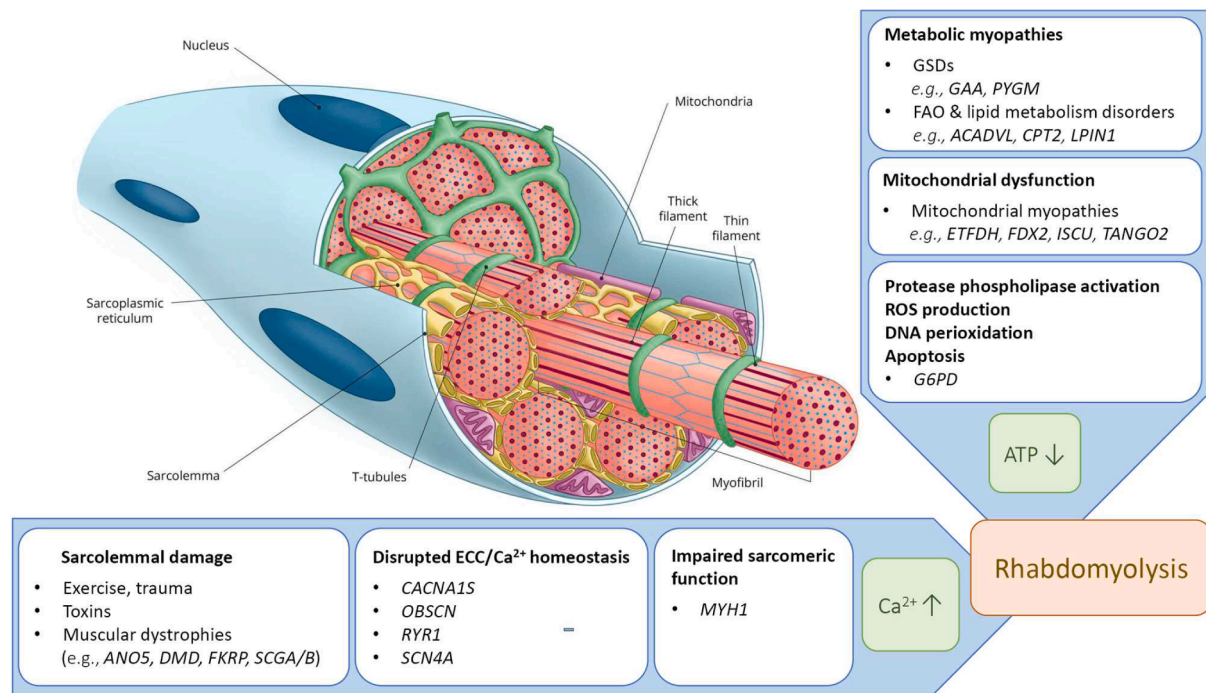
Fig. 3. Major contributors to rhabdomyolysis focusing on genetic causes. Figure adapted from Cabrera-Serrano and Ravenscroft [98].

predominance of regenerating over necrotic fibers, reflecting the rapid progression of necrosis. However, muscle fiber necrosis and regeneration are not always found, likely due to sampling variability or differences in muscle involvement based on the etiology and specific trigger, such as strenuous exercise or trauma. In dystrophies associated with episodic rhabdomyolysis, such as FKRP deficiency, biopsy may show dystrophic changes even before clinical muscle weakness becomes evident, while metabolic disorders might display subtle glycogen or lipid deposits within muscle fibers. These findings can be useful for interpreting genetic variants linked to rhabdomyolysis. Muscle biopsy is particularly vital in mitochondrial myopathies, as mitochondrial DNA variants with low heteroplasmy may not be detected in blood samples. Here, biopsy provides a unique opportunity for biochemical, morphological, and genetic testing, often necessary for a precise diagnosis beyond identifying rhabdomyolysis alone.

Mads Godtfeldt Stemmerik (Denmark) presented the results of a study in which the proteomic response to an induced injury was examined in a group of subjects with different myopathies. Several muscular dystrophies are subject to an enhanced injury response and risk of ERM, yet our understanding of this response remains limited, primarily using CK and myoglobin as markers. The study included participants with Becker muscular dystrophy (BMD), Limb-girdle muscular dystrophy types R9 (*FKRP*) and R12 (*ANO5*), along with healthy controls. After an exercise challenge (cycling and leg strength tests), blood samples were analyzed with the SOMAscan 7 K platform to identify proteomic signatures [63]. Results revealed 32 common proteins elevated and one decreased at baseline in the BMD, ANO5, and FKRP groups compared to controls. Interestingly, only BMD and FKRP groups showed a significant response to exercise, with time-dependent protein changes peaking at 2–4 hours post-exercise. Further analysis showed that proteins linked to type II muscle fibers responded in these groups, unlike type I fibers. These findings suggest a common mechanism for muscle injury across different myopathies and highlight potential new biomarkers for distinguishing between cell membrane leaks and damage to contractile muscle elements.

Andreas Roos (Germany) discussed blood biomarkers in diagnosing rhabdomyolysis, with CK and myoglobin as the primary markers. Studies have also highlighted the potential of other proteins, noting

elevated serum cardiac troponin I (cTnI) in 21 % of rhabdomyolysis cases, particularly linked to substance abuse. These cases showed higher CK and creatinine levels compared to those without cTnI increase, although no correlation with the CK peak was found [64]. Elevation of aminotransferases was also shown in rhabdomyolysis-patients, which is not different according to concurrent liver disease [65]. Furthermore, serum gelsolin behaves differently in rhabdomyolysis than after acute tissue damage in other organs, such as liver necrosis and adult respiratory distress syndrome and thus might serve as a promising biomarker [66]. However, given that the non-cellular isoform of gelsolin is increased, altered serum level does not necessarily indicate muscle cell damage. Results of a meta-analysis of 14 papers revealed that serum lactate dehydrogenase may represent a prognostic indicator that can be used for stratification of patients at risk for rhabdomyolysis-induced ARF [67]. Further studies are needed to expand the catalogue of biomarkers related to the manifestation and clinical course of rhabdomyolysis and to define biomarker signature panels. The significant heterogeneity of rhabdomyolysis poses a major challenge in identifying these signatures.

Emily Oates (Australia) presented an overview of a new recently funded large cross-disciplinary Australian collaboration. Patients fulfilling at least one of the RHABDO-features [15] are likely to have one of the many monogenic genetic diagnoses that predispose to this condition. There are over 75 known rhabdomyolysis-associated genes, many of which encode important metabolic or muscle structural proteins. Importantly, there are well established treatment paradigms for a significant subset of the genetic rhabdomyolysis events. A specific example is the use of a medically prescribed restricted long-chain fat diet with supplemental medium chain triglycerides to reduce the risk and severity of rhabdomyolysis episodes in individuals with Very Long Chain Acyl Coa Dehydrogenase deficiency (VLCAD) biallelic disease-causing variants in *ACADVL* [68]. The impact of these diagnosis-specific treatments is life changing and in some circumstances lifesaving. The genetic diagnosis rate for suspected genetic rhabdomyolysis remains low, with only 18 % of 675 DNA samples analyzed via the Perth-based PathWest rhabdomyolysis panel yielding an informative result. This low diagnostic yield is hindering our ability to provide diagnosis-specific treatments. To improve genetic diagnosis rates in Australia, Oates' team has

developed a comprehensive diagnostic pipeline that integrates advanced genetic sequencing, analytical methodologies, and collaboration with clinicians and scientists. Key elements include: 1) whole genome sequencing for detecting causative variants in both nuclear and mitochondrial genomes, 2) advanced bioinformatic tools for variant detection and RNA/protein-level variant impact prediction, 3) a combination of established and emerging laboratory methods to functionally confirm candidate variants, 4) provision of clinically accredited genetic reports and treatment plans, and 5) incorporation of findings into clinical databases and publications. The results of these studies may be particularly beneficial for establishing a genetic diagnosis and improving clinical outcomes for patients and families affected by these conditions.

1.3. Session 3: the spectrum of ERM in athletes and military personnel

Francis O'Connor (USA) presented an overview of ERM in war fighters and athletes. ERM is a common clinical problem that confronts recreational, elite, and tactical athletes, as well as war fighters. In the American military, incidence rates have been identified at 36 to 43 cases per 100,000 person-years, while in athletes, the literature is robust with ERM cohort clusters, generally the result of unaccustomed exercise regimens [14,69]. Risk factors for ERM are well described, and include the classic description of doing 'too much, too soon, too fast'. Increasingly, however, the social dynamic of leadership and followership are being identified as culprits to ERM [70]. In addition to extreme exercise, clinicians who deal with athletes and war fighters need to be aware of the role of dietary supplements, and sickle cell trait (SCT) status. While SCT is generally benign, and does not preclude athletic participation, it has been demonstrated to have an increased relative risk of sudden death compared to athletes who do not carry SCT [71]. Exercise collapse associated with SCT has been described, and although a fairly uncommon presentation, it can result in a life-threatening ERM that requires prompt recognition, assessment and treatment [72]. ERM is treated supportively with attention to preventing ARF, and assessing for acute compartment syndrome; critically important is being cognizant of the role of gender, ethnicity, and physical fitness status in assessing CK levels [12,73,74]. Return to activity after ERM is generally unremarkable with the institution of progressive exercise [75]. In cases where ERM may be complicated by exertional heat illness, the American College of Sports Medicine has recently published new guidance on return to activity with an emphasis on the phased progression of exercise and environmental acclimatization [76]. In cases where the ERM presentation is unusual in its trigger, such as the result of accustomed exercise, recurrent, or associated with a family history of MH, exercise intolerance or cramping, referral should be considered with a neuromuscular specialist. Finally, for those cases that fail to recover and return to activity in a timely fashion, consultation should be considered with the appropriate specialist.

Sheila Riazi (Canada) presented the results of a study that compared the cellular aspects including calcium movement [77] and metabolomics [78] of patients with a history of a MH reaction, to the cellular aspects of MHS patients who had a history of recurrent rhabdomyolysis. Some patients with repeated rhabdomyolysis triggered by exercise and/or heat also test positive for MHS with genetic testing or with the In Vitro Contracture Test (IVCT), considered the gold standard diagnostic test for MHS. Patients with a history of an MH reaction may also show susceptibility to exertional or heat-induced rhabdomyolysis, and the majority of these patients carry variants in *RYR1* or *CACNA1S* [79]. The results of MHS patients with a history of an MH reaction or who had recurrent rhabdomyolysis were compared with normal control (MH negative) from cellular aspects, as well as magnetic resonance spectroscopy [80]. The results show that MH susceptible patients, regardless of the reason for referral (MH reaction or recurrent rhabdomyolysis), show similar pathophysiology at the cellular level, as well as both groups compared to healthy controls, show reduced ATP production from the oxidative pathway. Dantrolene, the drug used in intravenous

format to treat an MH reaction, can also be used successfully in oral format in much lower doses than is used for spasticity, to relieve muscle symptoms in MHS patients [43]. In addition, it can be used to reduce the severity and frequency of rhabdomyolysis in MH susceptible patients who carry variants in *RYR1* or *CACNA1S* [43].

1.4. Session 4: acute management of rhabdomyolysis

Gearoid M. McMahon (USA) presented a model that was developed to predict the risk of severe ARF in patients admitted to the hospital with rhabdomyolysis. ARF due to rhabdomyolysis (rhabdo-ARF) was first described in London in patients trapped under rubble after bombing raids [81]. Since then, the range of causes of rhabdo-ARF has expanded to include both traumatic (e.g., immobilization, vascular injury) and non-traumatic causes (e.g., infections, drugs, or inflammation) [82]. Approximately 26,000 cases are diagnosed annually in the United States, and rhabdo-ARF is more commonly diagnosed in males, those with a body mass index >40 kg/m^2 and individuals <10 and >60 years old [83]. While serum CK levels rise in all causes of rhabdomyolysis, this is not necessarily a good measure of ARF risk because there are situations where CK release can occur while the risk of ARF remains low. The cause of ARF in patients with rhabdomyolysis remains unclear but is thought to be due to a combination of renal vasoconstriction due to fluid sequestration, tubular obstruction by myoglobin and direct tubular toxicity of myoglobin metabolites [84]. CK release occurs commonly in patients following exercise and this is not commonly associated with ARF suggesting that CK itself is not a good measure of ARF risk. In one study of healthy college students asked to perform eccentric exercises with one arm, the mean CK four days post exercise was 6420 IU/L and 25 % had a CK >10,000 IU/L. None of these patients developed ARF [85]. This suggests that we need better ways of differentiating patients at higher risk from those who are unlikely to develop ARF. This would allow the triaging of patients in the emergency room and avoid unnecessary treatment. A study of 2371 patients with rhabdomyolysis constructed a risk score based on a variety of clinical and laboratory factors on admission to predict the likelihood of ARF requiring dialysis or dying [86]. The model included age on admission, serum levels of creatinine, calcium, phosphate, bicarbonate, and gender. But importantly, it also included etiology of the rhabdomyolysis with ERM patients in a lower risk category. This model was validated in an external dataset [87]. Given the low likelihood of adverse outcomes in patients with a low-risk score at hospital admission, this model could aid in decision making for physicians, prevent admissions to the hospital and lower overall healthcare costs.

John Vissing (Denmark) led the discussion on when to start treatment of patients with rhabdomyolysis. Most of the current literature dictates that swift and intensive rehydration treatment fluid therapy is essential to prevent ARF [10]. However, some advocate treatment to start when CK is as low as 1000–3000 [88,89]. Likely, treatment thresholds may be lower in patients with comorbidities, especially those that affect renal function, but is there any reason to treat NMD patients without comorbidities at such low CK values? Clearly, many NMD patients have chronic levels of CK around 5000–10,000 IU/L and yet do not suffer from ARF. Bosch et al. [1] reviewed the risk of developing rhabdomyolysis and ARF in patients without major comorbidities and found that the risk is very low when CK values are below 15,000–20,000 IU/L [1]. In addition, data from a chart review at Rigshospitalet in Copenhagen, examining patients with CK levels over 3000 IU/L. Among 701 patients, 240 had no comorbidities, and outcomes were similar for those with comparable CK levels, regardless of treatment. The study suggests that treating individuals with CK levels below 15,000 IU/L may be unnecessary. If treatment is initiated, it should focus on fluid replacement with saline and correcting electrolyte imbalances; bicarbonate infusion to alkalize urine lacks evidence. If compartment syndrome is suspected, pressure measurement is recommended before a potential fasciotomy is conducted. Recommendations for starting treatment for neuromuscular

disease without comorbidities include: **1)** CK levels over 20,000 IU/L, **2)** the presence of myoglobinuria, or **3)** an increase in creatinine of more than 26 mmol/L in 24 hours, or absolute levels exceeding 141 mmol/L.

Teerin Liewluck (USA) discussed the role of electrodiagnostic (EDX) testing relative to genetic testing and muscle biopsy in patients with rhabdomyolysis who have no clear acquired etiology, aiming to identify a possible underlying myopathy [90]. By reviewing an EDX database, 66 patients with rhabdomyolysis were identified in whom EDX was performed. Needle electromyography (EMG) revealed myopathic motor unit potential in 32 patients and normal motor unit potentials in 34 patients. The median time between the episode of rhabdomyolysis to EDX was 6 and 5.5 months in myopathic and normal EMG group, respectively. Muscle biopsy and genetic testing were performed in 41 and 37 patients, respectively. A diagnosis was established in 15 patients (11 myopathic EMG and 4 non-myopathic EMG; p=0.04), based on abnormal muscle biopsy (4/11 patients) or genetic testing (12/12 patients, encompassing five patients with normal muscle biopsy and 3 patients with normal EMG results). These included seven metabolic (including three individuals with a CPT2 deficiency, two with McArdle disease, one with TFP deficiency and one with an *MTCO1* mutation) and eight non-metabolic myopathies (three LGMD-R9, two LGMD-R12, and three *RYR1*-related myopathies). Genetic testing with NGS panels failed to identify the causative genes in 10/22 patients. In conclusion, myopathic EMG occurred in approximately half of patients with unprovoked rhabdomyolysis, more likely in patients with weakness and elevated CK at baseline. While patients with myopathic EMG were more likely to have non-metabolic myopathies, normal EMG did not exclude a myopathy, and genetic testing was primarily helpful to identify an underlying myopathy. It is recommended that in patients in whom genetic testing is performed, gene panels should include genes that are associated with metabolic myopathies, muscular dystrophies and disorders of excitation-contraction coupling.

1.5. Session 5: how to support and coach patients after rhabdomyolysis

Alejandro Lucia (Spain) provided a summary of rhabdomyolysis in the context of glycogen storage diseases. Individuals with GSD V or VII are at risk of developing rhabdomyolysis [91]. All physical activities from daily life activities to formal exercise might trigger this phenomenon, with the risk increasing with the intensity/duration of the relevant activity [91]. Acute stress situations (e.g., fever) are also potential triggers. There is a non-negligible risk for ARF, ranging from 6 % (Spain) [92] to 11 % (UK) [93] in GSD 5 associated with rhabdomyolysis. The medical recommendations for ARF prevention/management in patients with GSDV/VII are discussed in detail elsewhere and summarized herein [91]. First, caution is recommended when engaging physical activity that involves high mechanical stress (e.g., carrying/lifting heavy weights) and non-habitual tasks. Gradual familiarization with these activities is recommended together with prior carbohydrate ingestion—in the case of GSD 5 only—and sufficient hydration [91]. Patients with severe rhabdomyolysis should be treated with adequate fluid administration to prevent renal impairment or be put on dialysis if warranted [91]. For those who develop ARF, consultation with nephrology is required and hospital discharge is not recommended until a significant reduction of clinical symptoms, CK levels have normalized, and renal function tests are normal. There should also be a thorough evaluation with the patient as to why the episode occurred—with consideration of non-familiar tasks. Although no specific rehabilitation protocol can be proposed based on published data, the patient should not return to normal activity levels until the CK values and pain have returned to their baseline levels (≥1 week). Pain medication should be used sparingly (to avoiding masking the warning sign of pain) and treatment with non-steroidal anti-inflammatory drugs is discouraged. To avoid myoglobinuria episodes and subsequent ARF risk, strenuous exercise should be avoided but regular moderate exercise can be beneficial—including carefully, professionally supervised weight

training—among other reasons because it has been shown not to affect baseline CK while providing health and clinical benefits [94] and also preventing chronic kidney disease [95].

Nick Kruijt (The Netherlands) presented findings from a prospective online survey and retrospective medical record review of athletes and military personnel in The Netherlands who experienced exertional heat stroke or rhabdomyolysis between 2010 and 2020. The study evaluated prehospital management, risk factors, clinical features, and symptoms at six- and twelve-months post-event, including mental health issues. It found that prehospital care was inconsistent and often did not follow guidelines. Self-reported risk factors included poor acclimatization to heat (55 %) and peer pressure (28 %). Long-term symptoms included muscle issues at rest (26 %) or during exercise (28 %), and neurological sequelae (11 %). Validated questionnaires indicated severe fatigue (30 %) and mood/anxiety disorders (11 %). Additionally, 90 % of participants reported a lack of follow-up care, expressing that more frequent and intensive support would have aided their recovery. Our findings are highlighted by the recommendations of the American College of Sports Medicine on return to activity after ERM, as well as the more recent recommendations on return to activity after exertional heat stroke [96, 97].

2. Discussion

The 276th ENMC Workshop on ERM brought together an interdisciplinary group of experts to identify and address gaps in diagnosis and management of rhabdomyolysis. A critical area of focus was the compelling need for a standardized definition of and approach to rhabdomyolysis (Fig. 2). The group's consensus was that ERM should be diagnosed if there is a rapid increase in CK exceeding 10,000 IU/L. In non-exertional cases, a rapid increase in CK should exceed 5000 IU/L. If myoglobinuria is present, a diagnosis of rhabdomyolysis is established. In both exertional and non-exertional cases, clinical symptomology should include muscle swelling, weakness, or pain with CK levels reaching a maximum approximately 1–4 days after the inciting event. Additionally, CK levels should normalize within 1–2 weeks of rest, a key diagnostic feature. For patients with an underlying NMD condition, CK levels greater than 5–10 times the patient's baseline level should be considered indicative of rhabdomyolysis.

Clinicians must differentiate physiological responses to exercise from pathological rhabdomyolysis episodes, because mild to moderate CK elevations without systemic symptoms or complications may not require emergency care. The acute management of rhabdomyolysis was extensively discussed by the group and a tiered approach was recommended. Patients should be prioritized by red-flag symptoms, including abnormal vital signs, dark urine or anuria, compartment syndrome, or metabolic disturbances. Additionally, significant comorbidities may require greater caution and monitoring. The McMahon risk score is an effective tool for stratifying the risk of acute renal failure and guiding management[86]. While fluid resuscitation is the cornerstone of preventing acute renal failure, aggressive treatment in patients with CK levels below 15,000 IU/L and no comorbidities may not be necessary. Discussion during the workshop with evidence presented suggested that when the risk of renal complications in such patients is low, unnecessary interventions should be avoided.

The attendees also emphasized the importance of genetic evaluation in patients with recurrent or unexplained rhabdomyolysis. Early identification of hereditary causes of rhabdomyolysis allows for targeted management strategies, potentially reducing recurrent cases and improving long-term outcomes. The proposed RHABDO features (Box 1) were recommended to identify individuals for genetic testing for NMD and metabolic disorders. Further testing, including muscle MRI, serum biochemistry, exercise testing, muscle biopsy (>8 weeks after rhabdomyolysis), and broader genetic testing, can be conducted for inconclusive cases.

Prevention and recovery strategies were another focus of the

workshop. Specifically, there is a critical need for structured rehabilitation programs. Patients should be encouraged to gradually reintroduce physical activity at least four weeks after symptom resolution. Referrals to physical therapists and other specialists who frequently manage rhabdomyolysis patients should be placed to aid with long-term physical and psychological sequelae. Prevention should start with proper hydration and nutrition and avoiding unaccustomed or high-risk activities such as exercise involving eccentric muscle contractions. In addition, the importance of optimizing and mitigating high risk external factors as best as possible should be emphasized, such as hot and humid conditions, infection prior to performing exercise, or intake of potentially thermoregulatory modulating medications. Patients should be educated on recognizing early signs of rhabdomyolysis to receive timely evaluation. For those with specific NMD, management can be further tailored, such as in McArdle disease by modifying diet and exercise intensity or in *RYR1*-related rhabdomyolysis by avoiding extreme temperatures.

Future directions for investigation included standardizing diagnostic definitions of rhabdomyolysis to minimize variability in clinical practice and research, expanding biomarkers beyond CK and myoglobin to aid in diagnosis, risk stratification, and management, and continuing to identify monogenic and oligogenic risk factors. These priorities aim to improve diagnostic and therapeutic precision for this heterogeneous condition.

The workshop established critical guidance on diagnosis, management, and prevention of rhabdomyolysis. The recommendations aim to improve the identification of at-risk patients, optimize outcomes, personalize acute care, and enhance long-term quality of life for patients worldwide.

3. Conclusion

During the workshop, an overview of clinical and diagnostic aspects of ERM was made. In the acute phase, it is important to assess which patients require hospital admission. The acute management of patients with rhabdomyolysis includes a stepwise approach: **1)** when to refer a patient to the emergency room? **2)** when to admit a patient to the hospital? **3)** what is the risk of developing ARF? At a later timepoint, genetic testing should be considered.

Rhabdomyolysis is a condition relevant to many disciplines, and therefore crucial for every physician to know that it can occur in anyone who is exposed to unaccustomed exercise and/or other triggers, even in otherwise healthy, well-trained individuals. The significant impact on quality of life emphasizes that evaluating both physical and psychological long-term symptoms at a later timepoint is of great importance.

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Declaration of competing interest

None of the authors have any conflicts of interest to declare for this report.

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